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 DE-A- 2 758 104  
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CHEMICAL ABSTRACTS, vol. 92, no. 11,  
 March 17, 1980, Columbus, Ohio, US; UEDA,  
 IKUO: "3-(Substituted  
 piperidino)carbonylmethyl-5-chloro-2-benzo-  
 thiazolinones" page 592, column 2, abstract-  
 no. 94 383b

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CHEMICAL ABSTRACTS, vol. 75, no. 23, December 6, 1971, Columbus, Ohio, US; UMIO,  
SUMINORI et al.: "Heterocyclic fatty acid  
amides" page 324, column 1, abstract-no.  
140 834y

CHEMICAL ABSTRACTS, vol. 66, no. 21, May  
22, 1967, Columbus, Ohio, US; CHUGAI  
PHARMACEUTICAL CO., LTD.:  
"2-Benzothiazolinone derivatives" page 8903,  
column 1, abstract-no. 95 030]

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**Description**

This invention relates to novel benzothiazolinone derivatives, their production and pharmaceutical composition. The compounds of the invention are useful as antiallergic or anti-inflammatory agents.

5 Certain 3-substituted-carbonyl(lower)alkyl-2-benzothiazolinones such as 5-chloro-3-(4-hydroxypiperidinocarbonylmethyl)benzothiazolin-2-one are known as anti-allergic agents (see US-A-3,755,327).

Chemical Abstracts, vol. 66, 1967, abstract No. 65030j describes 2-benzothiazolinone derivatives, which are useful as an analgesic and antispasmodic.

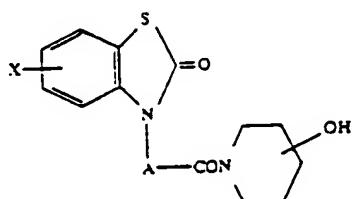
10 Chemical Abstracts, vol. 75, 1971, abstract No. 140834y relates to heterocyclic fatty acid amides, which are useful as central nerve depressants, anodynes and anti-inflammatory drugs.

Chemical Abstracts, vol. 92, 1980, abstract No. 94383b relates to 3-(Substituted piperidino)-carbonylmethyl-5-chloro-2-benzothiazolinones, which possess anti-asthma activity.

US-A-4 131 681 discloses compounds of the formula

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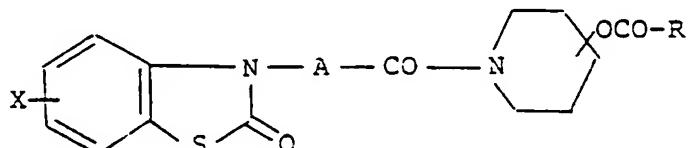


25 wherein A is a lower alkylene and X is halogen. These compounds have been found to be useful as anti-allergic agents.

This invention provides a benzothiazolinone derivative of the formula (I):

30

(I)



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in which A is a straight chain or branched chain alkylene group containing 1 to 6 carbon atoms; X is a halogen atom, R is the group -OR<sup>1</sup>, -NR<sup>2</sup>R<sup>3</sup> or -R<sup>4</sup>-COOH wherein R<sup>1</sup> is a straight chain or branched chain alkyl group containing 1 to 6 carbon atoms, R<sup>2</sup> and R<sup>3</sup> are a hydrogen atom or a straight chain or branched chain alkyl group containing 1 to 6 carbon atoms, and R<sup>4</sup> is a straight chain or branched chain alkylene group containing 1 to 6 carbon atoms or a straight chain or branched chain alkenylene group containing 2 to 6 carbon atoms and pharmaceutically acceptable salt thereof.

The invention also provides the production and pharmaceutical composition of the above mentioned compounds.

In the above formula (I),

45 the symbols A and R<sup>4</sup> mean a straight chain or branched chain alkylene group containing 1 to 6 carbon atoms, such as methylene, ethylene, propylene, trimethylene, tetramethylene, pentamethylene or hexamethylene.

The symbol R<sup>4</sup> means a straight chain or branched chain alkenylene group containing 2 to 6 carbon atoms, such as vinylene, propenylene, butenylene, pentenylene, hexenylene or 2-methyl-3-but enylene.

50 The symbols R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> mean a straight chain or branched chain alkyl group containing 1 to 6 carbon atoms, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl or tertiary butyl. The halogen atom for the symbol X may be fluoroine, chlorine, bromine or iodine atom.

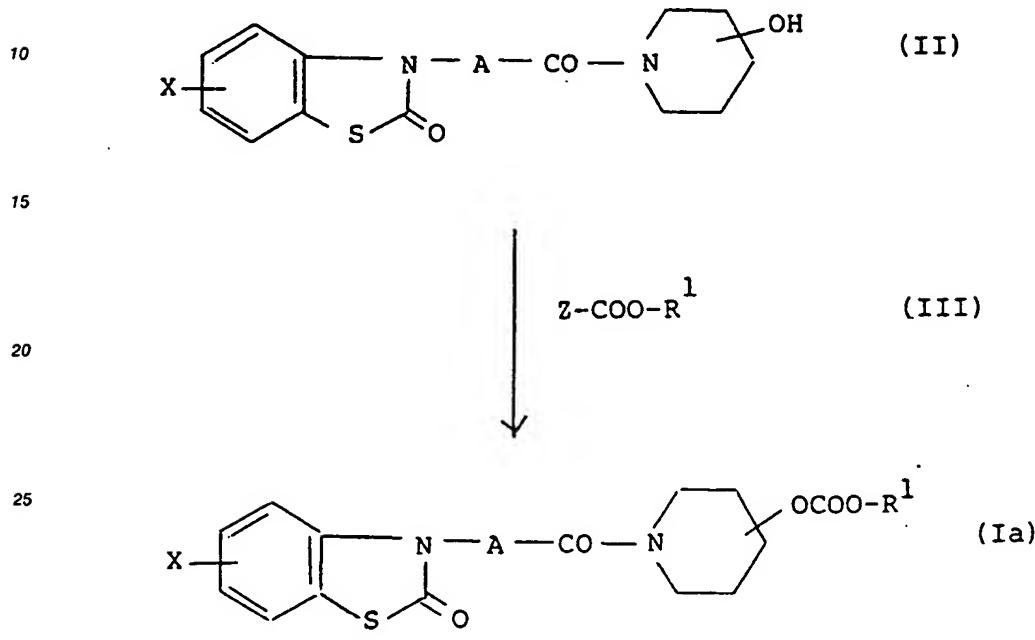
A preferred alkylene group is methylene group and a preferred halogen atom is chlorine atom which 55 can exist at the 4, 5, 6 or 7th position of the benzothiazoline ring. Preferred examples of the group -OCO-R in the formula (I) are ethoxycarbonyloxy, N-methylcarbamoyloxy, N-ethylcarbamoyloxy, N,N-dimethylcarbamoyloxy, carbamoyloxy, carboxyethylcarbonyloxy and carboxyvinylcarbonyloxy, which are preferred to be at the 3 or 4th position of the piperidine ring.

Examples of the pharmaceutically acceptable salts of the benzothiazolinone derivatives (I) include alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as calcium salt and magnesium salt and ammonium salt.

The benzothiazoline derivative (I) can be prepared by the following methods.

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**Preparation method 1 :**



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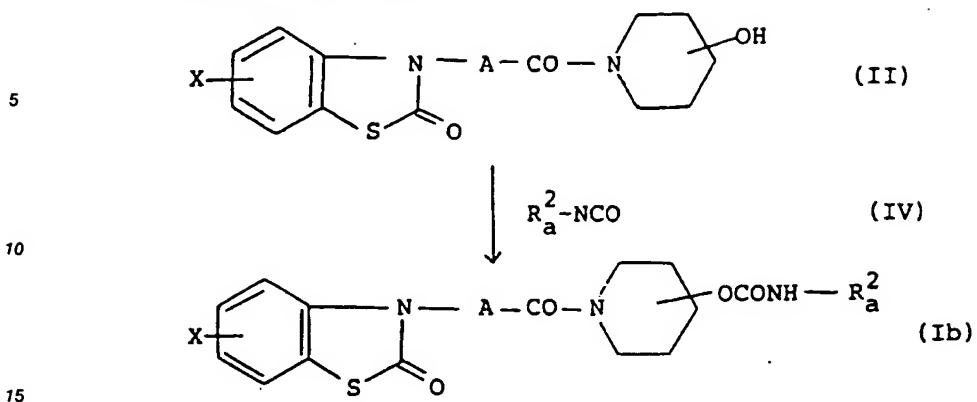
40

45

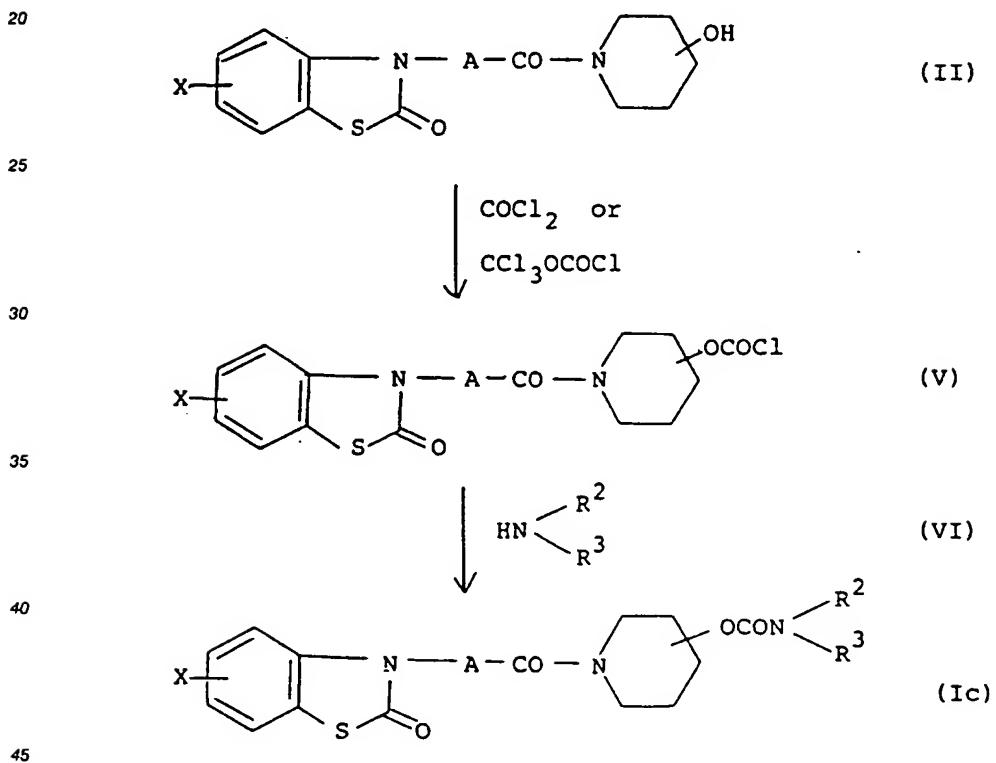
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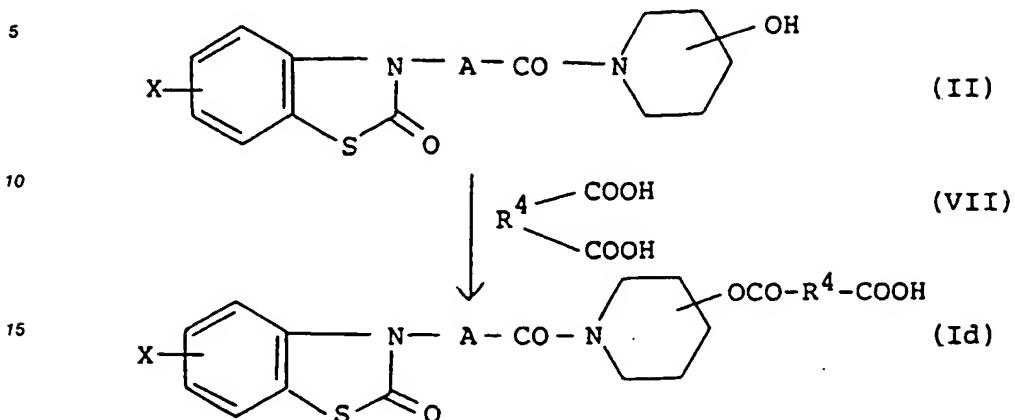
### Preparation method 2:



### **Preparation method 3:**



#### Preparation method 4:



In the above reaction formulae, the symbols A, X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> have the same meanings as defined above, Ra<sup>2</sup> is a lower alkyl group and Z is a halogen atom.

Details of the above mentioned methods are as follows.

## 25 Preparation method 1:

The benzothiazolinone derivative (**Ia**) can be prepared by reacting the starting compound (**II**) or its salt with the starting compound (**III**).

The compound (II) can be prepared by the method disclosed in US-A-3,755,327.

30 Examples of the salts of the starting compound (II) include alkali metal salts such as sodium salt, potassium salt and lithium salt.

Examples of the halogen atoms for Z of the starting compounds (III) include the same atoms as defined above.

This reaction can be generally carried out in a solvent such as pyridine, dimethylaniline, trimethylamine, dioxane, tetrahydrofuran or N,N-dimethylformamide with warming or heating.

#### **Preparation method 2:**

The benzothiazolinone derivative (Ib) can be prepared by reacting the starting compound (II) or its salt with the starting compound (IV).

This reaction can be generally carried out in a solvent such as pyridine, tetrahydrofuran, dioxane or N,N-dimethylformamide with warming or heating.

### **Preparation method 3:**

**45** The benzothiazolinone derivative (**Ic**) can be prepared by reacting the starting compound (**II**) or its salt with phosgene or trichloromethylchloroformate to obtain the intermediate (**V**) , followed by the reaction with

Examples of the salts of the starting compound (VI) include salts with inorganic acids such as

The first stage in the above reactions can be generally carried out in a solvent such as dioxane,

The second stage can be also generally carried out in a solvent such as dioxane, tetrahydrofuran or N,N-dimethylformamide with warming or heating. When the salt of the starting compound (VI) is used in this stage, the reaction is carried out in the presence of a base such as sodium hydroxide, potassium hydroxide, pyridine, trimethylamine, triethylamine or 4-dimethylaminopyridine.

#### Preparation method 4:

The benzothiazolinone derivative (Id) and its salt can be prepared by reacting the starting compound (II) with the starting compound (VII) or its reactive derivative.

Examples of the reactive derivatives of the starting materials (VII) include acid halides, acid active esters, acid anhydride and the like.

5 This reaction can be generally carried out in the presence of a base such as sodium hydroxide, potassium hydroxide, pyridine, trimethylamine, triethylamine or 4-dimethylaminopyridine, in a solvent such as tetrahydrofuran, dioxane or N,N-dimethylformamide with warming or heating.

The object compounds obtained by the above methods can be isolated and purified in a conventional manner.

10 The benzothiazoline derivatives (Ia), (Ib), (Ic), and (Id) all are included in the object compounds (I). Consequently, the salts of the benzothiazolinone derivatives (I) as exemplified above are applicable to the salts of the benzothiazolinone derivatives (Id).

15 The benzothiazolinone derivatives (I) and pharmaceutically acceptable salts thereof may be administered in the form of conventional pharmaceutical preparations suitable for oral or parenteral administration or topical application, such as capsules, granules, powders, tablets, ointments, syrups, injections, suppositories, aerosols, inhalants or eye drops. These pharmaceutical preparations may be prepared in a conventional method, using conventional additives for preparations.

20 Examples of the additives for preparations include carriers such as sucrose, lactose, glucose, starch, D-mannitol, D-sorbitol, crystalline cellulose, hydroxypropyl starch, talc, sodium hydrogenphosphate and calcium carbonate; binders such as methylcellulose, ethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, methylmethacrylate-methacrylic acid copolymer, gelatin, gum arabic, sucrose and starch; disintegrating agents such as starch, carboxymethyl cellulose or its calcium salt, hydroxypropyl cellulose with lower degree of substitution, croscarmellose sodium A type (Ac-Di-Sol)-hydroxypropyl starch, crystalline cellulose and sodium lauryl sulfate; lubricants such as magnesium stearate, calcium stearate, talc and hydrated silicon dioxide; corrigents such as citric acid, menthol, ammonium glycyrrhetinate, glycine and orange powders; preservatives such as sodium benzoate, sodium hydrogen sulfite, methyl p-oxybenzoate and propyl p-oxybenzoate; stabilizers such as citric acid, sodium citrate and acetic acid; suspending agents such as methyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose or its calcium salt and crystalline cellulose; dispersing agents such as polysorbate 80, Emalgen 30 408 (surfactant) and Emasol 310 (surfactant); solvents such as water; and bases such as cocoa butter, polyethyleneglycol, witepsol, white petrolatum and carboxyvinyl polymer.

30 These additives can be suitably chosen depending on the nature of the preparations.

35 The administration dosages of the benzothiazolinone derivatives and salts thereof are varied considerably taken into account the age and symptom of the subject and the manner for administration. When administered by oral route, injection or inhalation, the most suitable dosage can be chosen from the range of 0.1 to 1000 mg/kg/day, preferably 0.25 to 200 mg/kg/day. When administered topically by ointment, inhalation, etc. the dosage is determined considerably taken into account absorption by the tissue of the active ingredient from the preparation. Examples of dosage units of tablets are 50, 100, 200 mg, etc.; injections in intravenous route 12.5, 25 mg, etc. and that in subcutaneous route or in intramuscle route 15, 40 30 mg, etc.; suppository about 500 mg; and ointment about 100 to 2000 mg.

In addition to the compounds which will be described in the following examples, interesting compounds of the invention may be listed as follows.

4-chloro-3-(4-ethoxycarbonyloxy)piperidinocarbonylmethyl)benzothiazolin-2-one,  
 6-chloro-3-(4-ethoxycarbonyloxy)piperidinocarbonylmethyl)benzothiazolin-2-one,  
 45 7-chloro-3-(4-ethoxycarbonyloxy)piperidinocarbonylmethyl)benzothiazolin-2-one,  
 4-chloro-3-[4-(N-methylcarbamoyloxy)piperidinocarbonylmethyl]benzothiasolin-2-one,  
 6-chloro-3-[4-(N-methylcarbamoyloxy)piperidinocarbonylmethyl]benzothiazolin-2-one,  
 7-chloro-3-[4-(N-methylcarbamoyloxy)piperidinocarbonylmethyl]benzothiazolin-2-one,  
 4-chloro-3-[4-(N-ethylcarbamoyloxy)piperidinocarbonylmethyl]benzothiazolin-2-one,  
 50 6-chloro-3-[4-(N-ethylcarbamoyloxy)piperidinocarbonylmethyl]benzothiazolin-2-one,  
 7-chloro-3-[4-(N-ethylcarbamoyloxy)piperidinocarbonylmethyl]benzothiazolin-2-one,  
 4-chloro-3-(4-carbamoyloxy)piperidinocarbonylmethyl) benzothiazolin-2-one,  
 6-chloro-3-(4-carbamoyloxy)piperidinocarbonylmethyl) benzothiazolin-2-one,  
 7-chloro-3-(4-carbamoyloxy)piperidinocarbonylmethyl) benzothiazolin-2-one,  
 55 4-chloro-3-[4-(N,N-dimethylcarbamoyloxy)piperidinocarbonylmethyl]benzothiazolin-2-one,  
 6-chloro-3-[4-(N,N-dimethylcarbamoyloxy)piperidinocarbonylmethyl]benzothiazolin-2-one,  
 7-chloro-3-[4-(N,N-dimethylcarbamoyloxy)piperidinocarbonylmethyl]benzothiazolin-2-one,  
 3-[1-(4-chloro-2-oxobenzothiazolin-3-yl-acetyl)piperidin-3-yl-oxycarbonyl]propionic acid,

3-[1-(6-chloro-2-oxobenzothiazolin-3-yl-acetyl)piperidin-3-yl-oxy carbonyl]propionic acid,  
 3-[1-(7-chloro-2-oxobenzothiazolin-3-yl-acetyl)piperidin-3-yl-oxy carbonyl]propionic acid,  
 3-[1-(4-chloro-2-oxobenzothiazolin-3-yl-acetyl)piperidin-4-yl-oxy carbonyl]propionic acid,  
 3-[1-(6-chloro-2-oxobenzothiazolin-3-yl-acetyl)piperidin-4-yl-oxy carbonyl]propionic acid,  
 5 3-[1-(7-chloro-2-oxobenzothiazolin-3-yl-acetyl)piperidin-4-yl-oxy carbonyl]propionic acid,  
 3-[1-(4-chloro-2-oxobenzothiazolin-3-yl-acetyl)piperidin-4-yl-oxy carbonyl]acrylic acid,  
 3-[1-(6-chloro-2-oxobenzothiazolin-3-yl-acetyl)piperidin-4-yl-oxy carbonyl]acrylic acid and  
 3-[1-(7-chloro-2-oxobenzothiazolin-3-yl-acetyl)piperidin-4-yl-oxy carbonyl]acrylic acid  
 , and sodium or potassium salt thereof when carboxyl group is contained in the molecule of the above-  
 10 mentioned compounds.

## (Effect)

The antiallergic and anti-inflammatory activities of the benzothiazolinone derivative (I) of the invention  
 15 are described below.

Test Example 1

Antagonism to passive cutaneous anaphylaxis (P.C.A.) in rat:

20 Test method

Antiserum was prepared by the following method. One mg of egg albumin emulsified in 0.5 ml of Diphtheria-Pertussis-Tetanus Combined Vaccine (Tanabe Seiyaku Company Ltd.) and 0.5 ml of Freund's incomplete adjuvant (Seikagaku-Kogyo Company Ltd.) was used as the rat reaginic antiserum antigen  
 25 against egg albumin. The emulsion was given subcutaneously in a single dose of 1 ml divided equally (0.25 ml) to the four foot pads of male SLC Wistar-strain rats aged 7 weeks, each weighing 170 to 190 g. Blood samples were collected 12 days after injection and centrifuged at 3000 r.p.m. at 4°C for 15 minutes. The antisera thus obtained were stored at -20°C.

Groups consisting of five SLC Wistar-strain rats weighing 150 to 170 g were used. The rat reaginic antiserum against egg albumin was used at a dilution 1:4. The animals were sensitized with 0.1 ml of the antiserum injected intracutaneously on the depilated backs of the rats. Forty-eight hours after the injection of the antiserum, 1 ml of the mixture of egg albumin (5 mg) and Evan's blue (5 mg) in physiological saline (1 ml) was injected intravenously to cause the P.C.A. reaction. Thirty minutes after the injection of the antigen, animals were sacrificed and the skin was removed. The blue spots which occurred due to the P.C.A. reaction were measured their long and short diameters and the areas of the spots were found from the average of the values of the diameters. Each test compound was given orally with 16 mg/kg and intravenously with 4 mg/kg, 1 hour and 5 minutes before injection for P.C.A. reaction respectively. The reaction inhibitory ratio of the group administered the test compound was calculated from the ratio of the areas of the control group and the group administered the test compound. Test compounds are as follows.

Compound A: 3-[1-(5-chloro-2-oxobenzothiazolin-3-yl-acetyl)piperidin-4-yl-oxy carbonyl]propionic acid,  
 Compound B: 5-chloro-3-[4-ethoxycarbonyloxy piperidinocarbonylmethyl]benzothiazolin-2-one,  
 Compound C: 5-chloro-3-[4-(N-ethylcarbamoyloxy)piperidinocarbonylmethyl]benzothiazolin-2-one, and  
 Compound D: 5-chloro-3-[4-(N,N-dimethylcarbamoyloxy)piperidinocarbonylmethyl]benzothiazolin-2-one.

45 Test results

The results are shown by the following Table 1.

Table 1

| [P.C.A. reaction inhibitory ratio of rat (%)] |               |                     |                            |
|---|---------------|---------------------|----------------------------|
|   | Test compound | Oral administration | Intravenous administration |
| 5   | A             | 50.9                | 42.2                       |
|   | B             | 50.7                | 44.2                       |
| 10  | C             | 45.1                | 41.6                       |
|   | D             | 40.3                | 47.8                       |

Test Example 2

- 15 Antagonism to acute edema at sole of hind leg in rat:

Groups consisting of five SLC Wistar-strain rats weighing 150 to 170 g were used.

Each test compound was given orally with 200 mg/kg and intravenously with 64 mg/kg, 30 minutes and five minutes respectively before subcutaneous injection of a prophlogistic substance (1 ml of 1%  $\lambda$ -carrageenin solution) into the sole of one hind leg. A volume of the sole was measured with time. The edema ratio of sole edema was calculated in comparison between the volumes of the sole before and after injection of the prophlogistic substance. The inhibition ratio was calculated from the difference of the edema ratio between the substance administered group and the control group.

- 25 Test compounds

The compounds A and C in the test example 1 were used.

Results

- 30 The results are shown by the following Table 2.

Table 2

| Inhibitory ratio (%) of sole edema in rat |            |      |      |      |             |      |
|---|------------|------|------|------|-------------|------|
| Administrating route                      |            | Oral |      |      | Intravenous |      |
| Measuring time (hr.)                      |            | 1    | 2    | 3    | 1           | 2    |
| 35  | Compound A | 24.5 | 62.3 | 69.4 | 83.2        | 24.2 |
| 40  | Compound C | -    | -    | -    | 64.9        | 52.9 |

As clear from the above test results, the benzothiazolinone derivatives (I) of the present invention have excellent antiallergic and anti-inflammatory properties.

The benzothiazolinone derivatives (I) and their salts of the present invention possess not only antiallergic and anti-inflammatory properties but also blood platelets clotting inhibiting property and are useful as drugs for treating various diseases, e.g., bronchial asthma, allergic coryza, inflammatory diseases, dermatic diseases such as urticaria, or diseases caused by thrombus formed in brain and heart. Further, the benzothiazolinone derivatives (Id) show good water solubility and can be conveniently used for preparing liquid preparations such as a collunarium or an injection.

## (Examples)

- 55 This invention is illustrated in further detail by the following examples.

Example 1

Preparation of 5-chloro-3-(4-ethoxycarbonyloxy)piperidinocarbonylmethyl)benzothiazolin-2-one:

5-Chloro-3-(4-hydroxypiperidinocarbonylmethyl)benzothiazolin-2-one (3.2 g) was dissolved in dry pyridine (15 ml) and the solution was cooled. After ethyl chlorocarbonate (1.5 g) was dropwise added to the solution, the resultant was stirred for 8 hours at 80 °C. Pyridine was evaporated off under vacuum from the reaction mixture and the residue was recrystallized from a mixture of chloroform and ethanol to yield the title compound as colorless crystals (3.2 g). mp 196 - 197 °C

| Elemental analysis for C <sub>17</sub> H <sub>19</sub> N <sub>2</sub> O <sub>5</sub> SCI |           |                        |                      |                    |
|--|-----------|------------------------|----------------------|--------------------|
|  | Calcd (%) | C; 51.19,<br>C; 50.89, | H; 4.80,<br>H; 4.50, | N; 7.02<br>N; 7.05 |
| 10   |           |                        |                      |                    |

15 NMR(CDCl<sub>3</sub>)  
 $\delta$  : 1.35(3H,t,J = 7Hz), 1.55-2.30(4H,bs), 3.20-3.95(5H,bs), 4.22(2H,q,J = 7Hz), 4.69 (2H,s), 6.85-8.30-(3H,m)

#### Example 2

20 Preparation of 5-chloro-3-[4(N-methylcarbamoyloxy)piperidinocarbonylmethyl]benzothiazolin-2-one:

25 5-Chloro-3-(4-hydroxypiperidinocarbonylmethyl)benzothiazolin-2-one (3.2 g) was dissolved in dry pyridine (15 ml) and the solution was cooled. After methyl isocyanate (0.9 g) was dropwise added to the solution, the resultant was stirred for 15 hours at 30 °C. Pyridine was evaporated off under vacuum from the reaction mixture and the residue was recrystallized from methanol to yield the title compound as colorless crystals (2.7 g). mp 202 - 203 °C

| Elemental analysis for C <sub>16</sub> H <sub>18</sub> N <sub>3</sub> O <sub>4</sub> SCI |           |                        |                      |                      |
|--|-----------|------------------------|----------------------|----------------------|
|  | Calcd (%) | C; 50.07,<br>C; 49.98, | H; 4.73,<br>H; 4.50, | N; 10.95<br>N; 10.99 |
| 30   |           |                        |                      |                      |

35 NMR(CDCl<sub>3</sub>)  
 $\delta$  : 1.50-2.20(4H,bs), 2.75(3H,d,J = 5Hz), 3.10-3.90(5H,bs), 4.60(2H,s), 6.70-7.15 (4H,m)

#### Example 3

Preparation of 5-chloro-3[4(N-ethylcarbamoyloxy) piperidinocarbonylmethyl]benzothiazolin-2-one:

40 5-Chloro-3-(4-hydroxypiperidinocarbonylmethyl)benzothiazolin-2-one (3.2 g) was dissolved in dry pyridine (15 ml) and the solution was cooled. After ethyl isocyanate (0.9 g) was dropwise added to the solution, the resultant was stirred for 10 hours at 50 °C. Pyridine was evaporated off under vacuum from the reaction mixture and the residue was recrystallized from ethanol to yield the title compound as colorless crystals (3.0 g). mp 210 - 211 °C

| Elemental analysis for C <sub>17</sub> H <sub>20</sub> N <sub>3</sub> O <sub>4</sub> SCI |            |                      |                    |                    |
|--|------------|----------------------|--------------------|--------------------|
|  | Calcd. (%) | C;51.32,<br>C;51.11, | H;5.07,<br>H;4.74, | N;10.56<br>N;10.58 |
| 50   |            |                      |                    |                    |

NMR(CDCl<sub>3</sub>)  
 $\delta$  : 1.15(3H,t,J=7Hz), 1.50-2.20(4H,bs), 3.00-4.00 (7H,bs), 4.65 (2H,s), 6.80-7.25(4H,m)

#### Example 4

Preparation of 5-chloro-3-(4-carbamoyloxy)piperidinocarbonylmethyl)benzothiazolin-2-one:

A solution of 5-chloro-3-(4-hydroxypiperidinocarbonylmethyl)benzothiazolin-2-one (3.2 g) in dry dioxane (70 ml) was gradually dropped in a phosgene solution in dry dioxane (10 ml), under cooling. The mixture was left for two hours at room temperature. After cooling, to the mixture was gradually dropwise added 28% aqueous ammonia (5 ml) and the resultant was stirred for two hours at room temperature. Dioxane was evaporated off under vacuum from the reaction mixture. The residue was washed with water and then recrystallized from a mixture of dioxane and ethanol to yield the title compound as colorless crystals (2.8 g). m.p. 210 - 212°C

| Elemental analysis for C <sub>15</sub> H <sub>16</sub> N <sub>3</sub> O <sub>4</sub> SCl |                      |                    |                    |
|--|----------------------|--------------------|--------------------|
| Calcd. (%)   | C;48.72,<br>C;48.51, | H;4.36,<br>H;4.23, | N;11.36<br>N;11.39 |
|  |                      |                    |                    |

NMR(DMSO-d<sub>6</sub>)  
 $\delta$  : 1.10-2.30(4H,bs), 2.80-4.20 (5H,bs), 4.97 (2H,s), 6.49 (2H,s), 7.00-7.90 (3H,m)

#### Example 5

Preparation of 5-chloro-3-[4-(N,N-dimethyl carbamoyloxy)piperdinocarbonylmethyl]benzothiazolin-2-one:

A solution of 5-chloro-3-[4-hydroxypiperidinocarbonylmethyl]benzothiazolin-2-one (3.2 g) in dry tetrahydrofuran (60 ml) was cooled, to which a solution of trichloromethylchloroformate (0.61 ml) in dry tetrahydrofuran (2 ml) and a solution of triethylamine (1.4 ml) in dry tetrahydrofuran (4 ml) were dropwise added. After stirring for two hours at 60°C, the mixture was left overnight. After cooling the mixture, 50% aqueous dimethylamine (1.5 ml) was dropwise added to the mixture under stirring, followed by stirring for two hours at room temperature. Tetrahydrofuran was evaporated off under vacuum from the reaction mixture, and the residue was washed with water and then recrystallized from methanol to yield the title compound as colorless crystals (2.1 g). m.p. 148 - 150°C

| Elemental analysis for C <sub>17</sub> H <sub>20</sub> N <sub>3</sub> O <sub>4</sub> SCl |                      |                    |                    |
|--|----------------------|--------------------|--------------------|
| Calcd.   | C;51.32,<br>C;51.11, | H;5.07,<br>H;4.88, | H;10.56<br>N;10.68 |
|  |                      |                    |                    |

NMR(CDCl<sub>3</sub>)  
 $\delta$  : 1.50-2.20(4H,bs) , 2.90 (6H,s) , 3.20-4.00 (4H,bs) , 4.66 (2H,s) , 4.75-5.10 (1H,bs) , 6.80-7.40(3H,m)

#### Example 6

Preparation of 3-[1-(5-chloro-2-oxobenzothiazolin-3-yl-acetyl)piperidin-3-yl-oxy carbonyl]propionic acid:

A solution of 5-chloro-3-(3-hydroxypiperidinocarbonylmethyl)benzothiazolin-2-one (3.2 g) in dry pyridine (2.5 ml) and dry tetrahydrofuran (50 ml) was cooled. To the solution was dropwise added a solution of succinic anhydride (1.1 g) in dry tetrahydrofuran (5 ml) under stirring. The mixture was refluxed for two hours and then left overnight. The solvent was evaporated off under vacuum from the reaction mixture. The residue was dissolved in 5% aqueous sodium bicarbonate (20 ml). The resultant solution was cooled and adjusted to pH 2 with 1% hydrochloric acid. The precipitated crystals were collected by filtration, washed with water and then recrystallized from isopropyl alcohol to yield the title compound as colorless crystals (2.0 g). m.p. 131 - 133°C

| Elemental analysis for C <sub>18</sub> H <sub>19</sub> N <sub>2</sub> O <sub>6</sub> SCl |                      |                    |                  |
|--|----------------------|--------------------|------------------|
| Calcd.   | C;50.65,<br>C;50.39, | H;4.49,<br>H;4.25, | N;6.56<br>N;6.77 |
|  |                      |                    |                  |

NMR(DMSO-d<sub>6</sub>)  
 $\delta$  : 1.40-2.20(4H,bs), 2.62 (4H,s), 3.00-4.50 (5H,bs), 4.95 (2H,s), 6.90-7.90(3H,m) , 11.90 (1H,bs)

The above compound (1.0 g) was dissolved in a solution of sodium bicarbonate (0.2 g) in water (10 ml) and water was distilled off under vacuum at below 50°C to yield sodium salt of the title compound as colorless crystals.

NMR(DMSO-d<sub>6</sub>)

δ : 1.40-2.20 (4H,bs), 2.60 (4H,s), 3.00-4.50 (5H,bs), 4.93 (2H,s), 6.90-7.90 (3H,m)

Example 7

Preparation of 3-[1-(5-chloro-2-oxobenzothiazolin3-yl-acetyl)piperidin-4-yl-oxy carbonyl]propionic acid:

A solution of 5-chloro-3-(4-hydroxypiperidinocarbonylmethyl)benzothiazolin-2-one (3.2 g) in dry pyridine (2.5 ml) and dry tetrahydrofuran (50 ml) was cooled. To the solution was dropwise added a solution of succinic anhydride (1.1 g) in dry tetrahydrofuran (5 ml) under stirring. The mixture was refluxed for 2 hours and then left overnight. The reaction mixture was treated in the same manner as that in Example 6 to yield the title compound as colorless crystals (2.5 g).  
m.p. 154 - 156°C

| Elemental analysis for C <sub>18</sub> H <sub>19</sub> N <sub>2</sub> O <sub>6</sub> SCI |                      |                    |                  |
|--|----------------------|--------------------|------------------|
| Calcd. (%)   | C;50.65,<br>C;50.54, | H;4.49,<br>H;4.37, | N;6.56<br>N;6.53 |
|  |                      |                    |                  |

NMR(DMSO-d<sub>6</sub>)

δ : 1.25-2.20(4H,bs), 2.53 (4H,s), 3.10-4.00 (5H,bs), 4.96(2H,s), 7.15-7.85 (3H,m), 11.90(1H,bs)  
The above compound was treated with sodium bicarbonate in the same manner as that in Example 6 to yield sodium salt of the title compound as colorless crystals.

NMR(DMSO-d<sub>6</sub>)

δ : 1.25-2.20 (4H,bs), 2.50 (4H,s), 3.10-4.00 (5H,bs), 4.92 (2H,s), 7.15-7.85 (3H,m)

Example 8

Preparation of 3-[1-(5-chloro-2-oxobenzothiazolin3-yl-acetyl)piperidin-4-yl-oxy carbonyl]acrylic acid:

A solution of 5-chloro-3-(4-hydroxypiperidinocarbonylmethyl)benzothiazolin-2-one (3.2 g) in dry pyridine (2.5 ml) and dry tetrahydrofuran (50 ml) was cooled, to which a solution of maleic anhydride (1.0 g) in dry tetrahydrofuran (5 ml) was gradually dropwise added under stirring. The mixture was refluxed for two hours and then left overnight. The solvent was evaporated off under vacuum from the reaction mixture, and the residue was dissolved in 5% aqueous sodium bicarbonate (20 ml). The solution was cooled and adjusted to pH 2 with 1% hydrochloric acid. The precipitated crystals were collected by filtration, washed with water and then subjected to chromatography on silica gel eluting with ethanol/benzene (1:1). The solvent was evaporated off under vacuum from the eluate at below 50°C. The residue was recrystallized from isopropyl alcohol to yield the title compound as colorless crystals (2.1 g). m.p. 197 - 198°C

| Elemental analysis for C <sub>18</sub> H <sub>17</sub> N <sub>2</sub> O <sub>6</sub> SCI |                      |                    |                  |
|--|----------------------|--------------------|------------------|
| Calcd. (%)   | C;50.89,<br>C;50.63, | H;4.03,<br>H;4.21, | N;6.59<br>N;6.72 |
|  |                      |                    |                  |

NMR(DMSO-d<sub>6</sub>)

δ : 1.50-2.30 (4H,bs), 3.10-4.10 (5H,bs), 4.95 (2H,s), 5.87 (1H,d,J = 12Hz), 6.55 (1H,d,J = 12Hz), 7.10-7.80 (3H,m), 11.90 (1H,bs)

The above compound was treated with sodium bicarbonate in the same manner as that in Example 6 to yield sodium salt of the title compound as colorless crystals.

NMR(DMSO-d<sub>6</sub>)

δ : 1.50-2.30 (4H,bs), 3.10-4.10 (5H,bs), 4.97 (2H,s), 5.89(1H,d,J = 12Hz), 6.57 (1H,d,J = 12Hz), 7.10-7.80 (3H,m)

Example 9

|   |  |
|---|--|
| 5      3-(1-(5-chloro-2-oxobenzo<br>thiazolin-3-yl-acetyl)piperidin-4-yl-oxy carbonyl)propionic acid (referred to as<br>Compound A hereafter)<br>Lactose<br>Hydroxypropyl cellulose<br>Starch | 500 (parts by weight)<br><br>9250 "<br>200 "<br>50 " |
| 10  |  |

The above ingredients were blended and granulated in a conventional manner into granules.

Example 10

|  |  |
|--|--|
| 20      5-Chloro-3-[4-(N,N-dimethyl carbamoyloxy)piperidinocarbonyl<br>methyl]benzothiaolin-2-one (referred to as Compound D hereafter)<br>Lactose<br>Hydroxypropyl cellulose<br>Starch<br>Crystalline cellulose | 500 (parts by weight)<br><br>8500 "<br>200 "<br>500 "<br>300 " |
| 25   |  |

25      The above ingredients were blended and granulated in a conventional manner into small grains.

Example 11

|                    |  |            |                       |            |        |                    |      |
|--------------------|--|------------|-----------------------|------------|--------|--------------------|------|
| 30                 | <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Compound A</td><td style="width: 50%;">500 (parts by weight)</td></tr> <tr> <td>D-mannitol</td><td>1987 "</td></tr> <tr> <td>Magnesium stearate</td><td>13 "</td></tr> </table> | Compound A | 500 (parts by weight) | D-mannitol | 1987 " | Magnesium stearate | 13 " |
| Compound A         | 500 (parts by weight)  |            |                       |            |        |                    |      |
| D-mannitol         | 1987 "   |            |                       |            |        |                    |      |
| Magnesium stearate | 13 "   |            |                       |            |        |                    |      |
| 35                 |  |            |                       |            |        |                    |      |

35      The above ingredients were blended and filled in hard gelatin-capsules, in a conventional manner, to give capsules, each of which contains 50 mg of Compound A.

Example 12

|                         |   |            |                       |         |        |             |      |                         |       |                 |      |
|-------------------------|---|------------|-----------------------|---------|--------|-------------|------|-------------------------|-------|-----------------|------|
| 40                      | <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Compound A</td><td style="width: 50%;">500 (Parts by weight)</td></tr> <tr> <td>Sucrose</td><td>9250 "</td></tr> <tr> <td>Citric acid</td><td>20 "</td></tr> <tr> <td>Hydroxypropyl cellulose</td><td>200 "</td></tr> <tr> <td>Sodium benzoate</td><td>50 "</td></tr> </table> | Compound A | 500 (Parts by weight) | Sucrose | 9250 " | Citric acid | 20 " | Hydroxypropyl cellulose | 200 " | Sodium benzoate | 50 " |
| Compound A              | 500 (Parts by weight)   |            |                       |         |        |             |      |                         |       |                 |      |
| Sucrose                 | 9250 "  |            |                       |         |        |             |      |                         |       |                 |      |
| Citric acid             | 20 "  |            |                       |         |        |             |      |                         |       |                 |      |
| Hydroxypropyl cellulose | 200 "   |            |                       |         |        |             |      |                         |       |                 |      |
| Sodium benzoate         | 50 "  |            |                       |         |        |             |      |                         |       |                 |      |
| 45                      |   |            |                       |         |        |             |      |                         |       |                 |      |

The above ingredients was blended in a conventional manner to make a dry-syrup.

Example 13

|  |                         |
|--|-------------------------|
| 5-Chloro-3-[4-(N-ethylcarbamoyloxy)piperidinocarbonylmethyl]benzothiazolin-2-one (referred to as Compound C hereafter) | 10000 (parts by weight) |
| Lactose  | 3000 "                  |
| Croscarmellose sodium A type(Ac-Di-Sol)  | 3000 "                  |
| Hydroxypropyl cellulose  | 1800 "                  |
| Magnesium stearate   | 200 "                   |

5 The above ingredients were blended and compressed, in a conventional manner, into tablets, each of  
10 which contains 100 mg of Compound C.

Example 14

|   |                         |
|---|-------------------------|
| 15 Compound A   | 20000 (parts by weight) |
| Lactose   | 10400 "                 |
| Hydroxypropyl cellulose with lower degree of substitution | 3600 "                  |
| Hydroxypropyl cellulose                                   | 1800 "                  |
| Magnesium stearate  | 200 "                   |

20 The above ingredients were blended and compressed, in a conventional manner, into tablets, each of  
which contains 200 mg of Compound A and then the tablets were coated with film-coating, in a conventional  
manner, to give film-coated tablets.

25 Example 15

|  |                       |
|--|-----------------------|
| 30 5-Chloro-3-(4-ethoxycarbonyloxy)piperidinocarbonylmethyl)benzothiazolin-2-one (referred to as Compound B) | 5000(parts by weight) |
| Lactose  | 4200 "                |
| Hydroxypropyl cellulose with lower degree of substitution  | 1100 "                |
| Hydroxypropyl cellulose  | 600 "                 |
| Magnesium stearate   | 100 "                 |

35 The above ingredients were blended and compressed, in a conventional manner, into tablets, each of  
which contains 50 mg of Compound B, and then the tablets were subjected to sugar-coating.

40 Example 16

|                         |                         |
|-------------------------|-------------------------|
| 45 Compound A           | 25000 (parts by weight) |
| Lactose                 | 14600 "                 |
| Crystalline cellulose   | 4700 "                  |
| Ethyl cellulose         | 300 "                   |
| Hydroxypropyl cellulose | 1800 "                  |
| Magnesium stearate      | 100 "                   |

50 The above ingredients were blended and granulated, in a conventional manner, into fast-soluble granules  
and sustained release granules.

These granules were compressed into tablets, each containing 250 mg of Compound A, and the tablets  
were subjected to film-coating in a conventional manner, to give film-coated sustained release tablets.

55 Example 17

|   |  |  |
|---|--|--|
| 5 | Compound A<br>Sodium bicarbonate<br>Citric acid<br>Methyl p-oxybenzoate<br>Propyl p-oxybenzoate<br>Sucrose | 1000 (parts by weight)<br>84 "<br>20 "<br>25 "<br>15 "<br>4500 " |
|---|--|--|

10 The above ingredients were dissolved in purified water to make a syrup of which total amount is 10,000 parts by weight.

Example 18

|    |   |   |
|----|---|---|
| 15 | Compound D<br>Citric acid<br>Crystalline cellulose<br>Methyl p-oxybenzoate<br>Propyl p-oxybenzoate<br>Sucrose | 1000 (parts by weight)<br>10 "<br>800 "<br>25 "<br>15 "<br>4500 " |
| 20 |   |   |

20 The above ingredients were suspended or dissolved in purified water to make a syrup of which total amount is 10,000 part by weight.

Example 19

|    |   |  |
|----|---|--|
| 30 | Compound A<br>Sodium hydroxide<br>Methyl p-oxybenzoate<br>Polysorbate 80<br>Lidocaine hydrochloride | 2500 (parts by weight)<br>40 "<br>10 "<br>10 "<br>50 " |
| 35 |   |  |

35 The above ingredients were dissolved in distilled water for injection to make injectable solution of which total amount is 10,000 parts by weight.

Example 20

|    |  |  |
|----|--|--|
| 40 | Compound A<br>White petrolatum<br>Sorbitan trioleate | 500 (parts by weight)<br>9025 "<br>475 " |
| 45 |  |  |

45 The above ingredients were blended and kneaded into ointment.

Example 21

50

55

5

|                       |                        |
|-----------------------|------------------------|
| Compound A            | 5000 (parts by weight) |
| White petrolatum      | 40000 "                |
| Sorbitan sesquioleate | 5000 "                 |
| Cetanol               | 18000 "                |
| Lauromacrogol         | 500 "                  |
| Butyl p-oxylenzoate   | 100 "                  |

The above ingredients were blended and kneaded into ointment.

10

Example 22

15

|             |                       |
|-------------|-----------------------|
| Compound A  | 250 (parts by weight) |
| Lactic acid | 250 "                 |

The above ingredients were blended and filled in capsules to give capsules, for inhalation, each of which contains 25 mg of Compound A.

20

Example 23

25

|                      |                       |
|----------------------|-----------------------|
| Compound A           | 100 (parts by weight) |
| Sodium bicarbonate   | 10 "                  |
| Polysorbate 80       | 40 "                  |
| Methyl p-oxybenzoate | 26 "                  |
| Propyl p-oxybenzoate | 14 "                  |

30

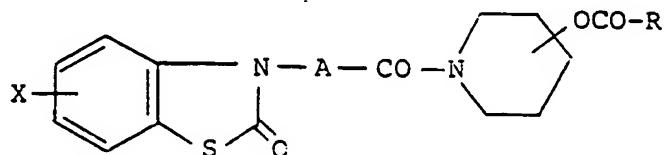
The above ingredients were dissolved in sterile purified water to make eyedrop of which total amount is 10,000 parts by weight.

**Claims**

35 **Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, NL, SE**

1. A benzothiazolinone derivative of the formula (I):

40



45

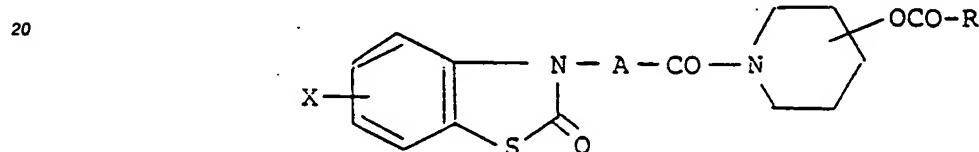
in which A is a straight chain or branched chain alkylene group containing 1 to 6 carbon atoms; X is a halogen atom, R is the group -OR<sup>1</sup>, -NR<sup>2</sup>R<sup>3</sup> or -R<sup>4</sup>-COOH wherein R<sup>1</sup> is a straight chain or branched chain alkyl group containing 1 to 6 carbon atoms, R<sup>2</sup> and R<sup>3</sup> are a hydrogen atom or a straight chain or branched chain alkyl group containing 1 to 6 carbon atoms, and R<sup>4</sup> is a straight chain or branched chain alkylene group containing 1 to 6 carbon atoms or a straight chain or branched chain alkenylene group containing 2 to 6 carbon atoms and pharmaceutically acceptable salt thereof.

2. A compound of claim 1 in which A is methylene group and X is chlorine atom.

55

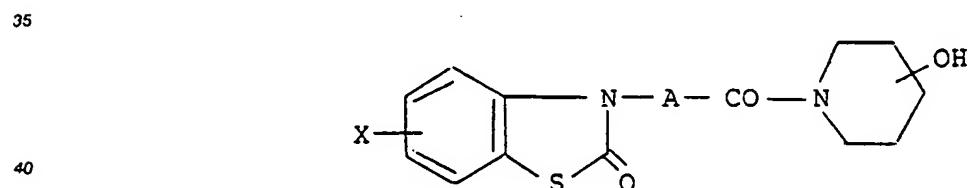
3. A compound of claim 1 in which the group -NR<sup>2</sup>R<sup>3</sup> is amino, methylamino, ethylamino or dimethylamino group.

4. A compound of claim 1 in which the group  $-R^4COOH$  is  $-CH_2CH_2COOH$  or  $-CH=CHCOOH$ .
5. A compound of claim 1 in which the group  $-OR^1$  is ethoxy group.
- 5 6. A compound of claim 1 which is 5-chloro-3-(4-ethoxycarbonyloxy)piperidinocarbonylmethyl)-benzothiazolin-2-one.
7. A compound of claim 1 which is 5-chloro-3-[4-(N-ethylcarbamoyloxy)piperidinocarbonylmethyl]-benzothiazolin-2-one.
- 10 8. A compound of claim 1 which is 5-chloro-3-[4-(N,N-dimethylcarbamoyloxy)piperidinocarbonylmethyl]-benzothiazolin-2-one.
- 15 9. A compound of claim 1 which is 3-[1-(5-chloro-2-oxobenzothiazolin-3-ylacetyl)piperidin-3-yloxycarbonyl]propionic acid or sodium salt thereof.
10. A process for preparing a benzothiazolinone derivative of the formula (I):



or pharmaceutically acceptable salt thereof, in which A is a straight chain or branched chain alkylene group containing 1 to 6 carbon atoms; X is a halogen atom, R is the group  $-OR^1$ ,  $-NR^2R^3$  or  $-R^4-COOH$  wherein  $R^1$  is a straight chain or branched chain alkyl group containing 1 to 6 carbon atoms,  $R^2$  and  $R^3$  are a hydrogen atom or a straight chain or branched chain alkyl group containing 1 to 6 carbon atoms, and  $R^4$  is a straight chain or branched chain alkylene group containing 1 to 6 carbon atoms or a straight chain or branched chain alkenylene group containing 2 to 6 carbon atoms, which comprises

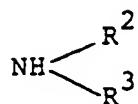
30 i) reacting a compound of the formula (II):



45 with a compound of the formula (III):  $Z-COOR^1$ , a compound of the formula (IV):  $Ra^2-NCO$  or a reactive derivative of a compound of the formula (VII):



55 or  
ii) reacting a compound of the formula (II) with phosgen or trichloromethylchloroformate, followed by the reaction with a compound of the formula (VI):



, wherein the symbols A, X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> have the same meanings as defined in the formula (I); R<sup>a2</sup> is a lower alkyl group and Z is a halogen atom, and  
10 iii) optionally converting the resultant which contains carboxyl group into pharmaceutically acceptable salt thereof.

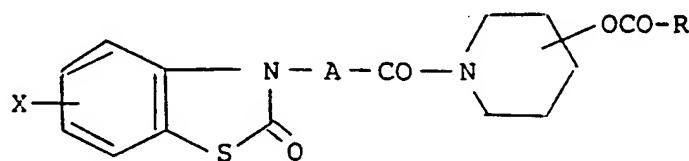
11. A pharmaceutical composition which comprises a compound of claim 1 as an active ingredient.

**Claim for the Contracting State : ES**

15

1. A process for preparing a benzothiazolinone derivative of the formula (I):

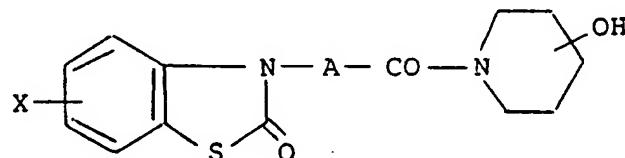
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25

or pharmaceutically acceptable salt thereof, in which A is a straight chain or branched chain alkylene group containing 1 to 6 carbon atoms; X is a halogen atom, R is the group -OR<sup>1</sup>, -NR<sup>2</sup>R<sup>3</sup> or -R<sup>4</sup>-COOH wherein R<sup>1</sup> is a straight chain or branched chain alkyl group containing 1 to 6 carbon atoms, R<sup>2</sup> and R<sup>3</sup> are a hydrogen atom or a straight chain or branched chain alkyl group containing 1 to 6 carbon atoms, 30 and R<sup>4</sup> is a straight chain or branched chain alkylene group containing 1 to 6 carbon atoms or a straight chain or branched chain alkenylene group containing 2 to 6 carbon atoms, which comprises  
i) reacting a compound of the formula (II):

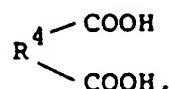
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40

with a compound of the formula (III): Z-COOR<sup>1</sup>, a compound of the formula (IV): Ra<sup>2</sup>-NCO or a reactive derivative of a compound of the formula (VII):

45

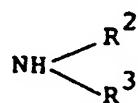


50

or

ii) reacting a compound of the formula (II) with phosgen or trichloromethylchloroformate, followed by the reaction with a compound of the formula (VI):

55



, wherein the symbols A, X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> have the same meanings as defined in the formula (I); R<sup>a</sup> is a lower alkyl group and Z is a halogen atom, and  
 iii) optionally converting the resultant which contains carboxyl group into pharmaceutically acceptable salt thereof.

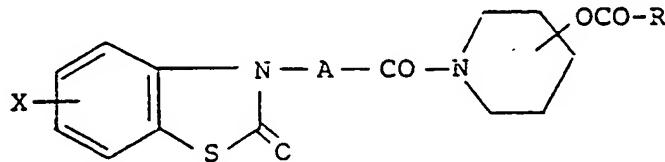
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**Patentansprüche****Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, NL, SE**

1. Benzothiazolinonderivat der Formel (I):

10

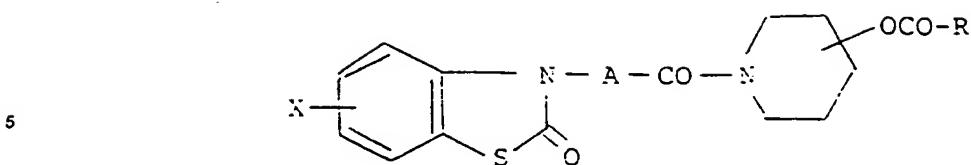
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20 worin A eine geradkettige oder verzweigtkettige Alkylengruppe, die 1 bis 6 Kohlenstoffatome enthält, bedeutet; X ein Halogenatom bedeutet; R die Gruppe -OR<sup>1</sup>, -HR<sup>2</sup>R<sup>3</sup> oder -R<sup>4</sup>COOH bedeutet, worin R<sup>1</sup> für eine geradkettige oder verzweigtkettige Alkylgruppe, die 1 bis 6 Kohlenstoffatome enthält, steht, R<sup>2</sup> und R<sup>3</sup> für ein Wasserstoffatom oder eine geradkettige oder verzweigtkettige Alkylgruppe, die 1 bis 6 Kohlenstoffatome enthält, stehen und R<sup>4</sup> für eine geradkettige oder verzweigtkettige Alkylengruppe, die 1 bis 6 Kohlenstoffatome enthält, oder eine geradkettige oder verzweigtkettige Alkenylengruppe, die 2 bis 6 Kohlenstoffatome enthält, steht; und die pharmazeutisch annehmbaren Salze davon.

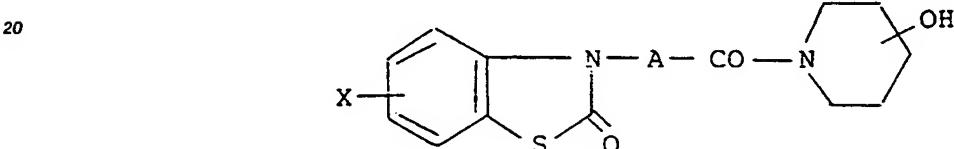
- 25
- 30 2. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß A eine Methylengruppe und X ein Chloratom bedeuten.
- 35 3. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß die Gruppe -HR<sup>2</sup>R<sup>3</sup> eine Amino-, Methylamino-, Ethylamino- oder Dimethylaminogruppe bedeutet.
- 40 4. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß die Gruppe -R<sup>4</sup>COOH -CH<sub>2</sub>CH<sub>2</sub>COOH oder -CH=CHCOOH bedeutet.
- 45 5. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß die Gruppe -OR<sup>1</sup> eine Ethoxygruppe bedeutet.
- 50 6. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß sie 5-Chlor-3-(4-ethoxycarbonyloxypiperidinocarbonylmethyl)-benzothiazolin-2-on ist.
7. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß sie 5-Chlor-3-[4-(N-ethylcarbamoyloxy)piperidinocarbonylmethyl]-benzothiazolin-2-on ist.
8. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß sie 5-Chlor-3-(4-(N,N-dimethylcarbamoyloxy)piperidinocarbonylmethyl)-benzothiazolin-2-on ist.
9. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß sie 3-[1-(5-Chlor-2-oxobenzothiazolin-3-yl-acetyl)-piperidino-3-yl-oxycarbonyl]-propionsäure oder das Natriumsalz davon ist.
- 55 10. Verfahren zur Herstellung eines Benzothiazolinonderivats der Formel (I):

55

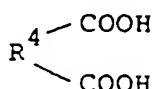


10 oder eines pharmazeutisch annehmbaren Salzes davon, worin A eine geradkettige oder verzweigtketige Alkylengruppe, die 1 bis 6 Kohlenstoffatome enthält, bedeutet; X ein Halogenatom bedeutet; R die Gruppe -OR<sup>1</sup>, -NR<sup>2</sup>R<sup>3</sup> oder -R<sup>4</sup>COOH bedeutet, worin R<sup>1</sup> für eine geradkettige oder verzweigtketige Alkylgruppe, die 1 bis 6 Kohlenstoffatome enthält, steht, R<sup>2</sup> und R<sup>3</sup> für ein Wasserstoffatom oder eine geradkettige oder verzweigtketige Alkylgruppe, die 1 bis 6 Kohlenstoffatome enthält, stehen und R<sup>4</sup> für eine geradkettige oder verzweigtketige Alkenylengruppe, die 2 bis 6 Kohlenstoffatome enthält, steht, dadurch gekennzeichnet, daß

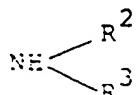
15 (i) eine Verbindung der Formel (II):



mit einer Verbindung der Formel (III): Z-COOR<sup>1</sup>, einer Verbindung der Formel (IV): Ra<sup>2</sup>-NCO oder einem reaktiven Derivat einer Verbindung der Formel (VII):



35 umgesetzt wird; oder  
 (ii) eine Verbindung der Formel (II) mit Phosgen oder Trichlormethylchlorformiat umgesetzt wird und anschließend mit einer Verbindung der Formel (VI):



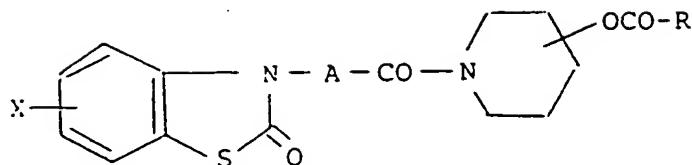
45 umgesetzt wird, worin die Symbole A, X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> die gleichen Bedeutungen, wie sie bei der Formel (I) gegeben wurden, besitzen; Ra<sup>2</sup> eine niedrige Alkylgruppe bedeutet und Z ein Halogenatom bedeutet; und  
 (iii) gegebenenfalls die entstehende Verbindung, die eine Carboxylgruppe enthält, in ein pharmazeutisch annehmbares Salz überführt wird.

50 11. Pharmazeutisches Präparat, dadurch gekennzeichnet, daß es eine Verbindung nach Anspruch 1 als aktiven Bestandteil enthält.

55 Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung eines Benzothiazolinonderivats der Formel (I):

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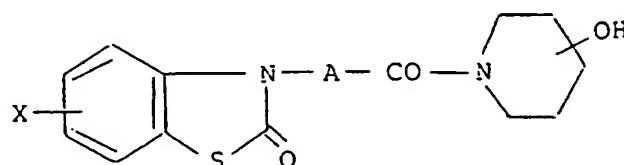
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oder eines pharmazeutisch annehmbaren Salzes davon, worin A eine geradkettige oder verzweigtkettige Alkylengruppe, die 1 bis 6 Kohlenstoffatome enthält, bedeutet; X ein Halogenatom bedeutet; R die Gruppe -OR<sup>1</sup>, -HR<sup>2</sup>R<sup>3</sup> oder -R<sup>4</sup>COOH bedeutet, worin R<sup>1</sup> für eine geradkettige oder verzweigtkettige Alkylgruppe, die 1 bis 6 Kohlenstoffatome enthält, steht, R<sup>2</sup> und R<sup>3</sup> für ein Wasserstoffatom oder eine geradkettige oder verzweigtkettige Alkylgruppe, die 1 bis 6 Kohlenstoffatome enthält, stehen und R<sup>4</sup> für eine geradkettige oder verzweigtkettige Alkylengruppe, die 1 bis 6 Kohlenstoffatome enthält, oder eine geradkettige oder verzweigtkettige Alkenylengruppe, die 2 bis 6 Kohlenstoffatome enthält, steht,  
dadurch gekennzeichnet, daß

15

(i) eine Verbindung der Formel (II):

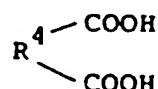
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mit einer Verbindung der Formel (III): Z-COOR<sup>1</sup>, einer Verbindung der Formel (IV): Ra<sup>2</sup>-NCO oder einem reaktiven Derivat einer Verbindung der Formel (VII):

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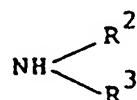


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umgesetzt wird; oder

(ii) eine Verbindung der Formel (II) mit Phosgen oder Trichlormethylchlorformiat umgesetzt wird und anschließend mit einer Verbindung der Formel (VI):

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umgesetzt wird, worin die Symbole A, X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> die gleichen Bedeutungen, wie sie bei der Formel (I) gegeben wurden, besitzen; Ra<sup>2</sup> eine niedrige Alkylgruppe bedeutet und Z ein Halogenatom bedeutet; und

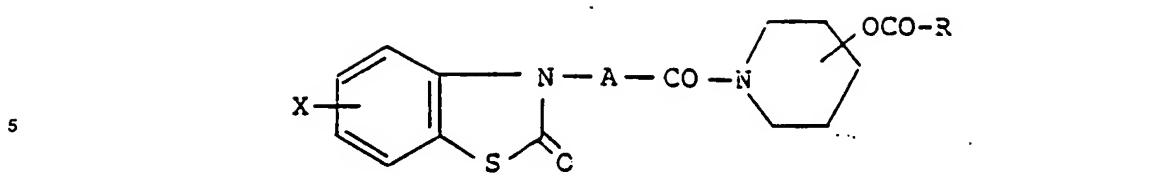
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(iii) gegebenenfalls die entstehende Verbindung, die eine Carboxylgruppe enthält, in ein pharmazeutisch annehmbares Salz überführt wird.

#### Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, NL, SE

55 1. Dérivé de benzothiazolinone de formule (I):



10 dans laquelle A est un groupe alkylène à chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone; X est un atome d'halogène; R est le groupe -OR<sup>1</sup>, -NR<sup>2</sup>R<sup>3</sup> ou -R<sup>4</sup>COOH dans lesquels R<sup>1</sup> est un groupe alkyle à chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone, R<sup>2</sup> et R<sup>3</sup> sont un atome d'hydrogène ou un groupe alkyle à chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone, et R<sup>4</sup> est un groupe alkylène à chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone, ou un groupe alkénylène à chaîne droite ou ramifiée contenant 2 à 6 atomes de carbone, et sel de celui-ci acceptable du point de vue pharmaceutique.

- 15
2. Composé suivant la revendication 1, dans lequel A est un groupe méthylène et X est un atome de chlore.
  - 20 3. Composé suivant la revendication 1, dans lequel le groupe -NR<sup>2</sup>R<sup>3</sup> est un groupe amino, méthylamino, éthylamino ou diméthylamino.
  4. Composé suivant la revendication 1, dans lequel le groupe -R<sup>4</sup>COOH est un groupe -CH<sub>2</sub>CH<sub>2</sub>COOH ou -CH = CHCOOH.

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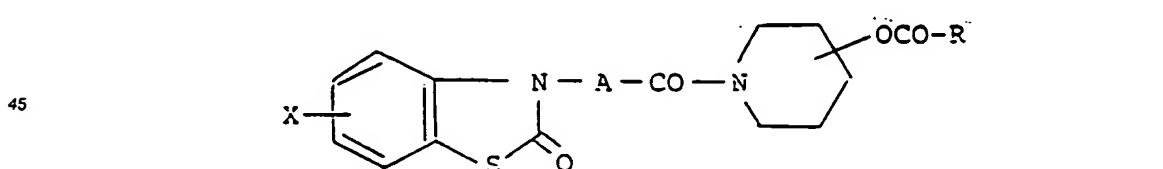
  5. Composé suivant la revendication 1, dans lequel le groupe -OR<sup>1</sup> est un groupe éthoxy,
  6. Composé suivant la revendication 1, qui est la 5-chloro-3-(4-éthoxycarbonyloxypipéridinocarbonylméthyl)benzothiazolin-2-one.

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  7. Composé suivant la revendication 1, qui est la 5-chloro-3-[4-(N-éthylcarbamoyloxy)-pipéridinocarbonylméthyl]benzothiazolin-2-one.
  8. Composé suivant la revendication 1, qui est la 5-chloro-3-[4-(N,N-diméthylcarbamoyloxy)-pipéridinocarbonylméthyl]benzothiazolin-2-one.

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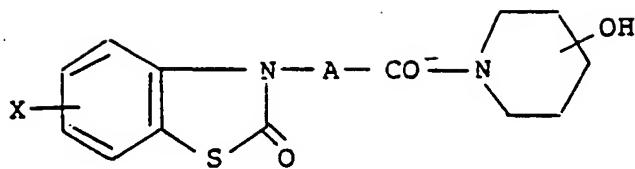
  9. Composé suivant la revendication 1, qui est l'acide 3-[1-(5-chloro-2-oxo-benzothiazolin-3-ylacétyl)-pipéridin-3-yl-oxy carbonyl]propionique ou son sel de sodium.
- 40 10. Procédé pour la préparation d'un dérivé de benzothiazolinone de formule (I):



50 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans laquelle A est un groupe alkylène à chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone; X est un atome d'halogène; R est le groupe -OR<sup>1</sup>, -NR<sup>2</sup>R<sup>3</sup> ou -R<sup>4</sup>COOH dans lesquels R<sup>1</sup> est un groupe alkyle à chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone, R<sup>2</sup> et R<sup>3</sup> sont un atome d'hydrogène ou un groupe alkyle à chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone, et R<sup>4</sup> est un groupe alkylène à chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone ou un groupe alkénylène à chaîne droite ou ramifiée contenant 2 à 6 atomes de carbone, qui comprend :

(i) la réaction d'un composé de formule (II) :

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avec un composé de formule (III) : Z-COOR<sup>1</sup>, un composé de formule (IV) : Ra<sup>2</sup>-NCO ou un dérivé réactif d'un composé de formule (VII) : R<sup>4</sup>(COOH)<sub>2</sub>, ou  
 (ii) la réaction d'un composé de formule (II) avec du phosgène ou du chloroformiate de trichlorométhyle, suivie de la réaction avec un composé de formule (VI) : HNR<sup>2</sup>R<sup>3</sup>,  
 dans lesquelles les symboles A, X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> sont tels que définis dans la formule (I); Ra<sup>2</sup> est un groupe alkyle inférieur et Z est un atome d'halogène; et  
 (iii) la conversion éventuelle du produit résultant qui contient un groupe carboxy en un sel de celui-ci acceptable du point de vue pharmaceutique.

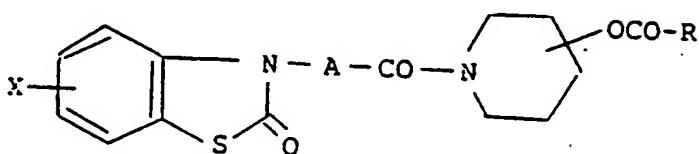
11. Composition pharmaceutique qui comprend un composé suivant la revendication 1 en tant que composant actif.

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**Revendication pour l'Etat contractant suivant : ES**

1. Procédé pour la préparation d'un dérivé de benzothiazolinone de formule (I):

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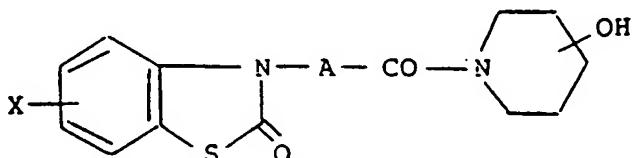


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ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans laquelle A est un groupe alkylène à chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone; X est un atome d'halogène; R est le groupe -OR<sup>1</sup>, -NR<sup>2</sup>R<sup>3</sup> ou -R<sup>4</sup>COOH dans lesquels R<sup>1</sup> est un groupe alkyle à chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone, R<sup>2</sup> et R<sup>3</sup> sont un atome d'hydrogène ou un groupe alkyle à chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone, et R<sup>4</sup> est un groupe alkylène à chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone, ou un groupe alkénylène à chaîne droite ou ramifiée contenant 2 à 6 atomes de carbone, qui comprend :

(i) la réaction d'un composé de formule (II):

40



45

avec un composé de formule (III) : Z-COOR<sup>1</sup>, un composé de formule (IV) : Ra<sup>2</sup>-NCO ou un dérivé réactif d'un composé de formule (VII) : R<sup>4</sup>(COOH)<sub>2</sub>, ou  
 (ii) la réaction d'un composé de formule (II) avec du phosgène ou du chloroformiate de trichlorométhyle, suivie de la réaction avec un composé de formule (VI) : HNR<sup>2</sup>R<sup>3</sup>,  
 dans lesquelles les symboles A, X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> sont tels que définis dans la formule (I); Ra<sup>2</sup> est un groupe alkyle inférieur et Z est un atome d'halogène, et  
 (iii) la conversion éventuelle du produit résultant qui contient un groupe carboxy en un sel de celui-ci acceptable du point de vue pharmaceutique.